The European Council`s Partial General Approach to the Proposal for a Medical Device Regulation: Its potential implications on demarcation, classification, and conformity assessment of substance-based medical devices

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

"Master of Drug Regulatory Affairs"

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Dr. Ruth Zeller-Adam

aus Kempten (Allgäu)

Bonn 2016

Betreuer und 1. Referent: Dr. Ehrhard Anhalt

Zweiter Referent: RA Michael Wimmer

Table of contents

COVER PAGE 1

TABLE OF CONTENTS 3

TABLE OF FIGURES 5

LIST OF ABBREVIATIONS 6

1 INTRODUCTION 7

1.1 Aims and objectives 8

2 DEMARCATION / SCOPE 9

2.1 Medical devices containing living organisms 9

2.2 Devices without an intended medical purpose 11

3 CLASSIFICATION 13

3.1 Classification rule 3 13

3.1.1 Example: devices affected by revised rule 3 14

3.2 Classification rule 13 15

3.2.1 Example: devices affected by revised rule 13 16

3.3 Proposed classification rule 19 18

3.3.1 Example: devices affected by proposed rule 19 19

3.4 Proposed classification rule 21 19

3.4.1 Example: devices affected by proposed rule 21, first indent 21

3.4.2 Example: devices affected by proposed rule 21, second indent 22

3.4.3 Example: devices affected by proposed rule 21, third indent 22

4 CONFORMITY ASSESSMENT 23

4.1 Conformity assessment procedures 23

4.2 Foreseen specific procedures 28

4.2.1 Clinical evaluation consultation 28

4.2.2 Scrutiny procedure 30

4.2.3 Consultation procedure for drug-device combination products 32
4.2.4 Procedures for devices incorporating material of biological origin 32
4.2.5 Procedures for substance-based medical devices that are absorbed by or locally dispersed in the human body 34

4.3 Example: presentation of a potential "worst case conformity assessment scenario" for a substance-based medical device 36

5 DISCUSSION 39

5.1 Timelines 39

5.2 Implementation of proposed changes concerning substance-based medical devices 40
5.2.1 Demarcation / Scope 40
5.2.2 Re-classification 41
5.2.3 Special procedures within the conformity assessment 45

6 CONCLUSION AND OUTLOOK 48

7 SUMMARY 50

8 REFERENCES 52

Table of figures

Figure 4.1-1: Conformity assessment procedure of class I substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text. 24

Figure 4.1-2: Conformity assessment procedure of class IIa substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text. 25

Figure 4.1-3: Conformity assessment procedure of class IIb substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text. 26

Figure 4.1-4: Conformity assessment procedure of class III substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text. 27

List of abbreviations

%	percent
acc.	according
AESGP	Association of the European Self-Medication Industry
a.m.	above mentioned
Art.	Article
ART	Assisted Reproduction Technologies
CE	Communauté Européenne / European Community
E. coli	*Escherichia coli*
EC	European Community
EEC	European Economic Community
EFTA	European Free Trade Association
e.g.	*exempli gratia* / for example
EMA	European Medicines Agency
EN	Europäische Norm / European Standard
EP	European Parliament
EU	European Union
FIDE	Federation of European Dental Industry
H2O2	hydrogen peroxide
HIV	Human Immunodeficiency Virus
HMPC	Committee on Herbal Medicinal Products
i.e.	*id est* / that is to say
ISO	International Standards Organization
IVF	In Vitro Fertilisation
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive 93/42/EEC
MDR	Medical Device Regulation
MEDDEV	Guidance series on medical devices
nm	nanometer
No.	number
pH	potential hydrogen
PMCF	Post-Market Clinical Follow-Up
PMS	Post Market Surveillance
ppb	parts per billion
ppm	parts per million
resp.	respective/respectively
rev.	revision
spp.	*species pluralis*
TSE	Transmissible Spongiform Encephalopathies
TÜV	Technischer Überwachungsverein / Technical Inspection Agency
µm	micrometer

1. Introduction

Currently, the European Directive 93/42/EEC [1] specifies the regulations for placing medical devices on the market. Though, the European medical device legislation is under complete revision. Based on the experiences gained since the coming into forces of the medical devices provisions in the mid 1990`s and accelerated by incidences like the PIP scandal, it is aimed to increase patients´ safety.

The official legislative procedure has been started in 2012, with the Proposal of the European Commission for a Medical Device Regulation (MDR). The Commission Proposal [2] has been intensively discussed and revised by the European Parliament. The Parliament´s MDR Amendments [3] has been adopted in the first reading in April 2014. Subsequently, as third institution involved, the European Council had to come up with its proposals for MDR modification. In June 2015 the Council reached a Partial General Approach, which was completed in September 2015 [4].

This was the basis for starting the trilogue discussions between Commission, Parliament, and Council, in order to reach an agreeable compromise.

The scope of the MDR shall comprise active and non-active medical devices. Additionally, a separate Regulation concerning In Vitro Diagnostics is discussed in parallel.

Substance-based medical devices represent a particular group within the broad range of medical devices. Their presentation, form, and formulation are often similar to that of medicinal products, although they completely meet the definition of a medical device. The principal mode of action of substance-based medical devices is neither pharmacological, nor immunological, or metabolic. In light of the legal wording, substance-based medical means a device that is composed of a substance or a combination of substances.

In European health care, substance-based medical devices play an important role. For example, in the Netherlands, the sales volume of substance-based medical devices has been doubled in the last few years. In Italy, 500 manufacturers sell about 56 million package units per year. This accounts for 16% of the total pharmaceutical and medical device market of the country (excluding cosmetic products, food supplements etc.) [5].

1.1 Aims and objectives

The present work focuses on the implications of the EU Council Proposal for a MDR modification (Partial General Approach) of 19th June 2015 and 21 September 2015 (Revision 1), respectively [4], on demarcation, classification, and conformity assessment of substance-based medical devices in comparison to the current requirements set out in Medical Device Directive 93/42/EEC (shortly referred to as MDD in the following). The MDR Proposal of the European Commission of 26th September 2012 and the Amendments of the European Parliament of 2nd April 2014 are taken into consideration as well and are discussed where deemed to be of interest.

Finally, potential timelines of the ongoing legislative procedure are presented and estimation is attempted to what extent the proposed regulatory changes relating to substance-based medical devices will be implemented in the final legal text of the MDR.

The present work is based on the situation as per 31 December 2015.

2. Demarcation / Scope

As the presentation of substance-based medical devices and medicinal products is rather similar, the demarcation between device and drug is usually based on the intended principal mode of action. Determination if the principal mode of action has to be considered as pharmacological, immunological, or metabolic, or not, is often subject to intense discussion between manufacturers, notified bodies, and authorities.

By way of derogation from the approach that the principal mode of action is the crucial criterion for demarcation between substance-based medical device and medicinal product, it is discussed to exclude products containing living organisms *per se* from the scope of the MDR (see section 2.1).

Furthermore, some products groups have been regulated in the past as medical devices, although they do not completely fulfill the definition of a medical device, e.g. few aesthetic products. Aesthetic products (i.e. without a medical claim) are usually regarded as cosmetics but if they are applied in an invasive manner, the definition of a cosmetic product is not fulfilled.

Thus, additional provisions regarding products that are not covered by the MDD so far have been included in Commission`s MDR Proposal, more to clarify the scope of the latter ensuring harmonised implementation than to substantially change the scope of the EU legislation. This also concerns some substance-based medical devices (see section 2.2).

2.1 Medical devices containing living organisms

A medical device can be any instrument, apparatus, appliance, software, material or other article (Art. 1, paragraph 2, MDD). In particular, the term "material" is not further specified and can be broadly interpreted. Furthermore, although not specifically named in the MDD, micro-organisms fall under the definition of "substance" in Directive 2001/83/EC [6], Art. 1, paragraph 3.

It is therefore reasonable to categorise products that contain micro-organisms and that fulfill the definition of a medical device as substance-based medical devices.

Today, it is accepted that living organisms such as bacteria can be certified as medical devices if their intended mode of action is not considered as mainly pharmacological, metabolic, or immunological, and if a medical purpose is claimed [7].

The best-known product group of substance-based medical devices containing living organisms is *Lactobacillus*-containing devices, especially for vaginal application.

However, such products will potentially be excluded from the scope of the MDR. According to Council`s Partial General Approach (Art. 1, paragraph 2, subparagraph f), the MDR shall not apply to *"products […] that contain or consist of viable biological substances or organisms, including living micro-organisms, bacteria, fungi, or virus in order to achieve or support the intended purpose of the product"*. Here, the Council follows the Commission Proposal in large parts.

The European Parliament adopted in the first reading a less definitive wording. Only products containing certain living organisms shall be excluded that achieve their intended purpose by pharmacological, immunological or metabolic means (Art. 1, paragraph 2, subparagraph f of the EP Proposal). The European Parliament justified its amendment as follows: *"A general exclusion of biological substances would result in a loss of safe and efficient medical devices existing on the market at present which will not be approved as medicinal products as they have no pharmacological, immunological or metabolic mode of action"* [8].

"'Intended purpose' means the use for which the device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements" (Art. 2 subparagraph 1, Council`s MDR Partial General Approach). The principal and a claimed ancillary mode of action belong to the term "intended purpose". As a consequence, products containing living organisms would be excluded from the medical device regulation even by the Parliament if an ancillary pharmacological, immunological, or metabolic effect is claimed.

Coming back to the medical use of *Lactobacillus spp*., comprehensive research has shown that the mode of action of these micro-organisms is rather complex. The effects of locally administered *Lactobacillus spp*. in maintaining/restoring vaginal health are considered to be mainly attributed to [9]:

1) Competitive adhesion to the vaginal mucosa resulting in inhibition of colonisation of pathogens
2) Production of lactic acid resulting in a physiologically low pH and subsequently preventing the colonisation and proliferation of pathogens
3) Production of antimicrobial compounds (e.g. Hydrogen peroxide (H2O2) or bacteriocins).

From a biochemical point of view, effects 1) and 2) cannot be regarded as pharmacological or metabolic effects. However, 3) – if regarded separately – would have to be regarded as pharmacological [7]. The clinical relevance of 3) in achieving the intended purpose is still subject to scientific discussions (e.g. in [10, 11]).

Furthermore, the effects of orally applied probiotics (mainly *Lactobacillus spp*.) on the local and systemic immune system have been investigated in numerous *in vitro* and *in vivo* studies. Strong evidence of an immunological mode of action has been revealed [12].

Concerning the demarcation of borderline products, the following is emphasised in MEDDEV 2.1/3 rev 3 [13]:

"Although the manufacturer's claims are important, it is not possible to place the product in one or other category in contradiction with current scientific data. Manufacturers may be required to justify scientifically their rationale for the qualification of their product."

Thus, if the respective EP Amendment will be included in the final MDR, proving the absence of any pharmacological, immunological, or metabolic effect of the living organisms involved in achieving the intended purpose of a device would be the challenge for the manufacturer.

Taking the three proposed wordings for the MDR into consideration, it seems predictable that at least certain products containing living organisms can no longer be regulated as substance-based medical devices with coming into force of the future MDR.

2.2 Devices without an intended medical purpose

By current legal definition in the MDD, medical devices have to have a medical claim, i.e. an intended medical purpose, such as diagnosis, monitoring, treatment, or alleviation of a disease or an injury, or the modification of the anatomy.

However, acc. to Commission`s Proposal some very-well established products should be regulated as medical devices although they do not fulfill the definition of a medical device because they do not have a medical claim or indication.

An important group of substance-based medical devices without medical claims are dermal fillers for cosmetic indications. Dermal fillers can be used for medical purposes (e.g. linear morphoea, HIV-associated lipoatrophy), but they are used much more frequently today for

anti-ageing procedures. It is important to note that the indication for treatment (medical versus non-medical) does not alter or mitigate the inherent risks of the procedure.

Dermal fillers are injected into the tissue, i.e. by way of a surgically invasive procedure, thus a regulation as cosmetic product is precluded: *"'cosmetic product' means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity […]"* (Cosmetic Regulation Art. 2, paragraph 1, subparagraph a [14]).

Furthermore, they do not act in a pharmacological, immunological, or metabolic manner; they are intended to act as filling material only. In summary, therefore it would be reasonable to categorise such products as medical devices.

The MDR Proposals intend to close the gap regarding devices without medical claims. It is stated in Council`s Partial General Approach that the regulation shall also apply to the groups of products without an intended medical purpose that are listed in Annex XV.

Dermal fillers are listed in proposed Annex XV. Likewise, the Parliament suggested that devices for aesthetic purposes should also fall within the scope of the regulation (Art. 1, paragraph 1, sub-paragraph 2 of EP`s Amendments).

3. Classification

All medical devices including substance-based medical devices shall be classified into classes I, IIa, IIb, or III according to their intended use claimed by the manufacturer and their inherent risks. This approach for classification of medical devices is implemented in the MDD, Article 9, and is also found in the MDR Proposals (Article 41).

Classification criteria are provided by the legislator generally enabling medical devices to be appropriately classified (Annex IX of MDD 93/42/EEC or Annex VII of Commission´s MDR Proposal, respectively).

In comparison to the classification criteria as set out in the MDD, some classification rules are proposed to be modified and new classification rules are introduced in the MDR Proposals. Regarding substance-based medical devices, the potential revision of classification rules 3 and 13 and implementation of classification rule 21 and even rule 19 on nanomaterials are of special interest.

In the following chapters examples of substance-based medical devices are presented that would be affected by the proposed classification criteria with regard to reclassification.

3.1 Classification rule 3

Classification rule 3 of the MDD addresses non-invasive medical devices intended for modifying the biological or chemical composition of human tissues, cells, blood, or other (body) liquids intended for transplantation of infusion into the body. These devices are currently classified as class IIb devices unless the modification comprises filtration, centrifugation of exchanges of gas or heat. In the latter cases, the devices are in class IIa.

MDD classification rule 3 can be found in either of the proposed MDR wordings. Additionally, the Commission expanded rule 3 over non-invasive devices intended to be used for in vitro fertilisation (IVF) or assisted reproduction technologies (ART) and proposed to classify them as class IIb.

This Commission Proposal was further revised by the Council; however, its Partial General Approach confuses the situation for the following substance-based medical devices, which shall be treated as high-risk devices:

"All non-invasive devices consisting of a substance or a mixture of substances intended to be used in vitro in direct contact with human cells, tissues or organs taken off from the

human body or with human embryos before their implantation or administration into the body are in class III."

3.1.1 Example: devices affected by revised rule 3

The proposed amendment of rule 3 as laid down in Council`s Partial General Approach particularises that substance-based medical devices intended for preservation, storage, or other direct contact with cells, tissues, organs, and embryos before their insertion in the human body shall be regarded as class III devices.

An added value of the proposed addendum to current rule 3 in the MDD is considered debatable.

Substance-based medical devices affected by revised rule 3 are rather limited. One example is the group of **organ preservation solutions**. With regard to the latter, a thorough discussion has already been taken place in the Manual on Borderline and Classification of Medical Devices [15]. Some agents for transport, nutrition and storage of organs intended for transplantation may be regulated as medical devices provided that they meet the definition of a medical device. However, according to the Manual on Borderline and Classification, agents for transport, nutrition and storage of organs intended for transplantation usually act through pharmacologic, immunologic or metabolic means. Therefore the assessment whether these products have only an ancillary pharmacological, immunological or metabolic action or not is a crucial element for the qualification of the product. The decision on demarcation should be made on a case by case basis taking into account the purpose of the inclusion of this substance into the product.

Provided that the solutions under assessment meet the definition of a medical device, it is clearly outlined that these substance-based medical devices usually are already classified as class III devices, according to either current rule 17 or rule 13, which is even more likely.

Moreover, classification rule 13 in its current or proposed version would overrule the provisions of the revised classification rule 3 by qualifying most organ preservation solutions as drug-device combination products with a pharmacological, immunological, or metabolic action ancillary to that of the device. Thus, the proposed revision of rule 3 regarding substance-based medical devices can be assessed as partly redundant. However, with proposed classification rule 3, the Council might intend to unequivocally lock the possibility to market such products as class IIa/IIb products.

Importantly, **haemodialysis concentrates** (class IIb medical devices), which comprise a major device group falling under the provisions of rule 3, are not affected by the proposed reclassification. The principle of haemodialysis involves diffusion of solutes across a semipermeable membrane during counter-current flow. Thus, the dialysis concentrate is separated from the circulating blood in the extracorporeal circuit by a membrane. As solute diffusion occurs from the blood towards the dialysis concentrate, the latter products don´t come in direct contact with blood cells.

3.2 Classification rule 13

The current wording of classification rule 13 in the MDD Annex IX is as follows:

"All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are in class III."

The Commission revised classification rule 13 as follows:

"Rule 13

All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive 2001/83/EC, including a medicinal product derived from the human blood or human plasma, with action ancillary to that of the device, are in class III."

Both Parliament and Council have agreed. Interestingly, compared to the MDD text, the clause *"which is liable to act on the human body"* has been excluded in the MDR Proposals.

According to the MDD, rule 13 only applies to devices in which an ancillary pharmacological, immunological, or metabolic action on the human body caused by the incorporated substance that can be considered as medicinal product is likely. Reversely, the wording of the MDD takes the situation into account that substances, which are considered as medicinal products if used separately, are incorporated in a medical device but they are neither likely nor intended to exert an ancillary action on the human body by pharmacological, immunological, or metabolic means. In the latter case, current rule 13 does not apply.

However, rule 13 in its current wording (MDD) has been inconsistently implemented in the different EU Member States. Some competent authorities don`t follow this scientific argumentation, mostly due to the wording of their national medical device laws. In many national laws the wording for *"which is liable to act on the human body"* reads, retranslated into English: *"and which can act on the human body".* [16].

The proposed wording of revised rule 13 leaves no scope for any inconsistent interpretations by different notified bodies or authorities but leads in parallel to a general categorisation of the products under discussion as high-risk devices. By exclusion of the a.m. clause in the planned MDR, the incorporation of a substance fulfilling the medicinal product definition as of Directive 2001/83/EC automatically results in a class III combination device, independent of the mode or extent of action the incorporated substance is exerting on the human body in the specific product of interest.

In rule 13 substance-based medical devices are not explicitly named. Nevertheless, a range of substance-based medical devices would be affected by re-classification according to the revised classification rule 13 (examples see next section).

3.2.1 Example: devices affected by revised rule 13

Dexpanthenol is an alcohol analogue of pantothenic acid and is very frequently used in products intended for topical use on skin, mucosa, or the cornea. It is a well-established ingredient in cosmetics, substance-based medical devices, and medicinal products. Various modes of action are described for dexpanthenol:

Due to its hygroscopic property, topical dexpanthenol acts as moisturiser by improving stratum corneum hydration and reducing transepidermal water loss.

Dexpanthenol is metabolised to pantothenic acid, which is involved in Coenzyme A synthesis. The latter in turn plays a role in the early steps of the synthesis of fatty acids and sphingolipids that help to support skin barrier function [17]. Moreover, in *in vivo* experiments activation of fibroblasts was seen [18]. If the product is not intended to be applied onto injured surfaces with a breached basal membrane, this activating effect that fulfills the definition of pharmacological means is not considered to be of relevance.

Interestingly, the dexpanthenol concentration in medicinal products is generally higher than 5% indicating that pharmacologically relevant effects occur in higher concentrations only. Anhalt (2007) referred to a respective German monograph on dexpanthenol (published in

February 1993) outlining that at least a 5 % dexpanthenol concentration is needed for effects on wound healing of skin and/or mucosal lesions [16].

The purpose that is usually intended by the addition of dexpanthenol to the composition of a substance-based medical device is moisturising and/or water loss reduction only. Respective suitable dexpanthenol concentrations are chosen by the manufacturers (often ~ 2%). Consistent with scientific argumentation, several competent authorities (e.g. Luxembourg) have agreed to classify nasal sprays containing dexpanthenol in concentrations up to 2% as class I medical devices.

Nevertheless, revised rule 13 in the MDR Proposals would apply to nearly all substance-based medical devices containing dexpanthenol, without taking into consideration the concentration and the corresponding scientifically justifiable and intended mode of action.

A further product group that would possibly be affected by re-classification due to the revised classification rule 13 is substance-based medical devices containing **Icelandic Moss** (mostly marketed as lozenges). These products are indicated for soothing of dry cough as Icelandic Moss contains mucoadhesive polysaccharides with an indirect hydrating effect and the ability to form a protective film onto the irritated mucous membranes of the mouth and throat. As this effect must be considered to be not pharmacological and/or metabolic but physical, such products are regulated as medical devices.

Additionally, Icelandic Moss contains aromatic and aliphatic lichen acids (2 to 3%), to which bactericidal and/or bacteriostatic properties are attributed. The therapeutic relevance of the lichen acids is however doubtful [19]. Even the EMA Committee on Herbal Medicinal Products (HMPC) concluded that the available data on pharmacological effects do not contradict the use as physical demulcent: *"Despite non-clinical data on several activities of the water extract and/or substances isolated thereof exist, a direct correlation of the test results (kind of extract, route of administration in vitro vs. in vivo) with the clinical situation is not possible. The reported pharmacological effects are not considered contradictory to the oral and oromucosal traditional use of herbal preparations of Lichen islandicus as a demulcent for the symptomatic treatment of irritations of oral and pharyngeal mucosa with associated dry cough"* [20]

Thus, although scientific data point towards a negligible pharmacological effect of Icelandic Moss when used in the oral cavity for symptomatic treatment of dry cough, by strict interpretation of the proposed wording of rule 13 in the MDR Proposals a re-classification could become necessary.

3.3 Proposed classification rule 19

A classification rule on nanomaterial has been introduced by the Commission, which classifies devices consisting of nanomaterial as class III unless the nanomaterial is encapsulated or bound in such a manner that it cannot be released into the patient's or user's body (Annex VII, rule 19 of Commission`s Proposal). This classification rule has been adopted by the Council without any changes.

The Commission and Council justify the inclusion of this classification rule by claiming that *"there is scientific uncertainty about the risks and benefits of nanomaterials used for medical devices. […] In the design and manufacture of medical devices, the manufacturers should take special care when using nanoparticles that can be released to the human body and those devices should be subject to the most severe conformity assessment procedure"* (Recital 13 of Council`s Partial General Approach).

Interestingly, as many medical devices contain nanomaterials, but do not pose any danger to the patient, the European Parliament has considered it sufficient to limit the classification rule to devices containing nanomaterial that is deliberately intended to be released into the human body (Annex VII, rule 19 of the EP Amendment).

Nanomaterial is consistently defined by the three institutions as natural, incidental, or manufactured material containing particles (in an unbound state, or as aggregate or agglomerate), of which 50 % or more have one or more external dimensions in the size range 1 to 100 nm (Art. 2 paragraph 1, subparagraph 15 of the Commission´s MDR Proposal).

In summary, the Council, in consistency with the Commission, would even like to classify devices as class III that potentially release incidental nanoparticles into the patient´s or user´s body.

The proposed general re-classification has been critisised by multiple non-political institutions including industry associations. For example, the Federation of European Dental Industry (FIDE) claims that almost all solid particulates contained in medical devices (fillers, pigments, absorbents ….) would be nanomaterials according to the proposed definition, as from a technical point of view, the generation of few amounts of nanoparticles during the manufacturing process (e.g. milling) cannot be precluded [21]. All of these devices would have to be classified as class III. "*It can be calculated that for particulate solids with an average particle size by weight in the range of 1 – 100 µm (as often used) only a few ppb or ppm by weight or volume of nanoparticles are sufficient that the*

particulate fulfill this criteria. […] there is no distinction between true nanomaterials (containing a high amount or all of particles in the nanorange) and other particulate solids safely used for hundreds of years or particulates to which the human beings have been exposed to since beginning (e.g. sand or other corrosion products from rocks e.g. iron oxides produced naturally by rusting)" [21].

As for rule 13, substance-based medical devices are not explicitly named but might be significantly affected by proposed rule 19 (examples are given in section 3.3.1).

3.3.1 Example: devices affected by proposed rule 19

Substance-based medical devices available on the European Market also include wound powders. The concerned products mainly consist of aluminium silicates. Silicate wound powders are intended to support wound healing of small wounds and abrasions by adsorbing exudates and wound fluid [22].

According to classification rule 4, first indent of the MDD, Annex IX, these products are currently marketed mainly as class I devices.

Intended powder particle size is not in a nanoscale. Nevertheless, the incidental formation of a low amount (from the weight point of view) of nanoparticle dust (which however represents a big number of particles and thus falls under Commission`s definition of nanomaterial), e.g. during milling, transportation and storage of the product, is assumed to possibly occur.

Solely the fact that the potential of minimal exposure of a patient or user to nanoparticles by administration of such a substance-based medical device cannot be completely excluded would lead to a classification as high-risk (class III) device.

3.4 Proposed classification rule 21

The proposed classification rule 21 is subject to intense discussions in the ongoing legislative procedure for the MDR in all involved parties, i.e. the European Commission, the European Parliament, and the EU Council.

The European Commission introduced classification rule 21 in their MDR Proposal of September 2012: *"Devices that are composed of substances or combination of substances*

intended to be ingested, inhaled or administered rectally or vaginally and that are absorbed by or dispersed in the human body are in class III".

The general classification of those devices as high-risk medical devices was introduced by the Commission to ensure a high level of safety of those products regardless of their qualification. Furthermore, treating substance-based medical devices that are introduced in the human body via ingestion, inhalation, or rectal or vaginal application and that are absorbed or dispersed as high-risk products should make allowance for the difficult borderline between those substance-based medical devices and medicinal products.

Within its first reading in April 2014, the Parliament rejected classification rule 21 but it was reintroduced by the Council. However, compared with the Commission proposal, classification rule 21 was modified, specified, and even expanded:

"Rule 21

Devices that are composed of substances or combinations of substances that are intended to be introduced into the human body via a body orifice, or applied on skin and that are absorbed by or locally dispersed in the human body are:

- *in class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose,*
- *in class III if they are intended to be introduced into the gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body,*
- *in class IIb in all other cases, except if they are applied on skin, in which case they are in class IIa."*

It can be summarised that a higher classification of substance-based medical devices is generally sought at least by the Commission and the Council. With classification rule 21 as proposed by the Council and in conjunction with the classification rules for invasive devices, the classification of substance-based medical devices as class I medical devices is widely precluded.

However, the proposed wording has to be assessed as rather vague at some points. In particular the term "locally dispersed in the human body" leaves room for interpretation.

Concerning rule 21, second indent, as proposed by the Council, it has to be noted that even products would be affected by re-classification as class III if their target location is the oral cavity or pharynx but they are intended to be swallowed afterwards (= introduction into

the gastrointestinal tract, e.g. gels for symptom alleviation of dry cough). The components are usually digested and their products of metabolism are then absorbed. Acc. to the MDD, such products are mainly classified as class I devices according to rule 5 (Annex IX of MDD) and are available on the market for years without any reported safety-relevant incidences. Thus, by re-classification, the regulatory effort for the manufacturers would markedly increase without significant positive impact or added value on the benefit-to-risk assessment.

3.4.1 Example: devices affected by proposed rule 21, first indent

There is only a low number of medical devices on the European market so far fulfilling the definition criteria addressed by proposed rule 21, first indent. Examples for such devices are orally applied **products containing cranberry and/or D-mannose for treatment of urinary tract infections**. After oral ingestion, the substances are absorbed, reach the circulation, and are then excreted via the kidneys into the human urinary bladder. They exert their clinical effect – which is claimed to be non-pharmacological – locally in the urinary bladder.

Bacteria including *E. coli* play a crucial role in the pathogenesis of lower urinary tract infections (UTI). The current hypothesis is that cranberries as well as free D-mannose molecules work principally by preventing the adhesion of type 1 and p-fimbriae strains (particularly from *E. coli*) to the urothelium. The substances truncate the receptor binding sites of the uropathogenic bacteria and thus, adhesion of the bacteria to the urothelium is inhibited subsequently. Complexes consisting of bacteria and mannose or cranberry, respectively, can be excreted via urine [23, 24].

The presented substance-based medical devices can currently be classified as class IIa or class IIb devices, depending on the duration of use (see rule 5, second or third indent of MDD Annex IX, respectively). The fact that the products initially have to be systemically absorbed by the human body in order to achieve the intended purpose at another site as the administration site, has not been part of the decision process on classification of these devices so far. Pursuant to classification rule 21 as proposed by the Council, the medical devices would be classified as class III products.

3.4.2 Example: devices affected by proposed rule 21, second indent

Under current legislation, **lactase-containing devices** for oral administration indicated for symptom alleviation in patients with lactose intolerance can be classified as class IIa medical devices in accordance with rule 5, second indent, of MDD Annex IX, if the devices are intended for short term use, i.e. continuous use less than 30 days.

After ingestion, the enzyme lactase as typical protein is degraded over time by peptidases in the gastrointestinal tract within the physiological digestive process. Resulting free amino acids can then be absorbed and become systemically available. Thus, such products fall under rule 21, second indent of Council`s Partial General Approach (Annex VII), since their products of metabolism (not the enzyme itself) are considered to be systemically absorbed. A reclassification as class III medical device would be the consequence.

3.4.3 Example: devices affected by proposed rule 21, third indent

Nasal sprays containing salt solutions (e.g. seawater), which are medical devices intended for use in the nasal cavity (= introduced into the human body via a body orifice), may be affected by reclassification due to rule 21, third indent. Currently, such nasal sprays can be classified as class I medical devices in accordance with rule 5, second indent, of MDD Annex IX if the devices are intended for short-term use.

However, spraying the solution into the nasal cavity fulfills the characteristics of a "local dispersion in the human body". Thus, nasal sprays containing salt solutions may be reclassified as class IIb medical devices according to the proposed amendments of the EU Council.

A further device group falling under the third indent of rule 21 is **mouth-rinse solutions** intended for gargling. For example, hyaluronic acid solutions are often used because of their ability to shield the mucosa from irritating substances in the oral cavity in patients with gingivitis or stomatitis. Similar to the nasal sprays discussed above, these products are currently categorised as class I substance-based medical devices.

By gargling, the solution is "locally dispersed" in the oral cavity. This would result in the need of re-classification as class IIb device according to Council`s partial General Approach.

4. Conformity assessment

Medical devices are not subject to any pre-market authorisation by a regulatory authority but to a conformity assessment which, for medium and high risk devices, involves an independent third party, known as notified body.

The purpose of the assessment is to demonstrate conformity with all essential requirements applicable for the specific device. After a successful conformity assessment procedure, the products are certified. Once certified, devices bear the CE marking which allows them to circulate freely in the EU/EFTA countries and Turkey.

Depending on the risk class, the conformity assessment procedures and the involvement of a notified body differ. The MDR Proposals follow the general lines of the current legislation.

As substance-based medical devices are able – depending on their characteristics – to be assigned to any risk class (but rarely to class I according to proposed wordings of Commission and Council), the various conformity assessment procedures can apply.

4.1 Conformity assessment procedures

In the Commission´s MDR Proposal, the conformity assessment procedures available for medical devices according to their risk class are described in article 42. The general approaches for conformity assessment don´t differ compared to the MDD. Both Parliament and Council followed Commission´s Proposal.

Concerning the present thesis that focusing on substance-based medical devices, type examination (Annex IX of the MDR Proposal) in conjunction with product conformity verification (Annex X of the MDR Proposal), i.e. product testing in the final production phase, either by checking all products or by means of statistically valid random samples [25], is generally not considered to be an appropriate procedure for substance-based medical devices. Testing of the final product usually renders a substance-based medical device unusable. Therefore, type examination and product conformity verification have not been included in the overviews on possible ways of conformity assessment of substance-based medical devices (figures 4.1-1 to 4.1-4).

The different conformity assessment procedures are laid down in detail in the Annexes of the MDR Proposal. Concerning substance-based medical devices, Annex VIII is most important.

The conformity assessment procedure for class I devices can be carried out, as a general rule, under the sole responsibility of the manufacturer in view of the low level of vulnerability associated with these products. The manufacturers declare the conformity of their products by issuing the EU declaration of conformity after compiling the technical documentation for the device. However, when class I devices have a measuring function (not relevant for substance-based medical devices) or are sold sterile, a notified body must verify the aspects related to the measuring function or to the sterilisation process (see figure 4.1-1).

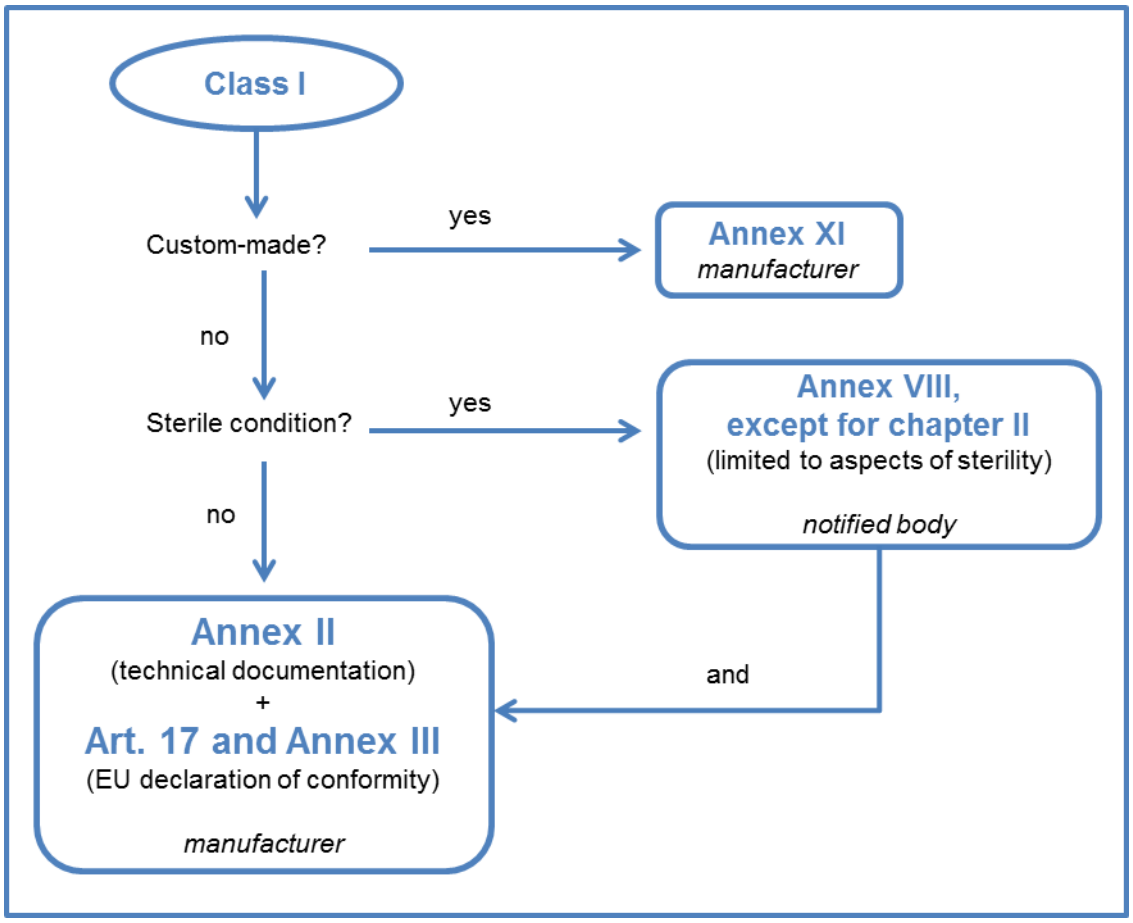

Figure 4.1-1: Conformity assessment procedure of class I substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text.

For devices of classes IIa, IIb and III, an appropriate level of involvement of a notified body is necessary.

In case of class IIa and IIb devices, the notified body checks the quality management system (e.g. compliance with the harmonised standard EN ISO 13485:2012 [26] plus additional requirements of the MDR) and, for representative samples, the technical documentation, which demonstrates compliance with all applicable essential requirements. Compared to Commission´s Proposal, the Council has streamlined and tightened the determination of technical documentation assessments. Regulatory ways of conformity assessment of class IIa and IIb substance-based medical devices as described in Council`s Partial General Approach are presented in figures 4.1-2 and 4.1-3.

Regarding manufacturers of class IIa devices, notified bodies shall execute assessments of design and technical documentation of at least one representative device for each category of devices.

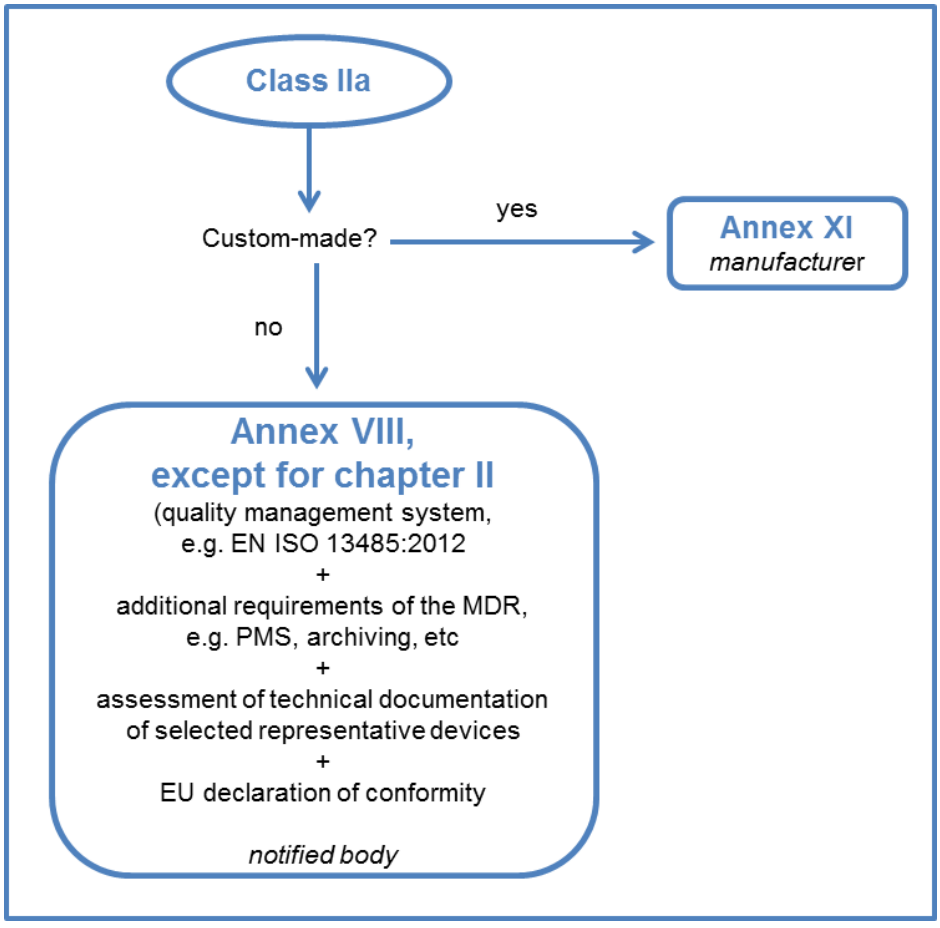

Figure 4.1-2: Conformity assessment procedure of class IIa substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text.

For class IIb devices, notified bodies` assessment of technical documentations shall comprise at least one representative device per generic device group. For this purpose, a generic device group means "*a set of devices having the same or similar intended purposes or commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics"* (Art. 2, paragraph 1, subparagraph 7 of Council`s Partial General Approach). Furthermore, it has been proposed by the Council that the requirements on technical documentation assessment of implantable class IIb devices should be the same as for class III devices.

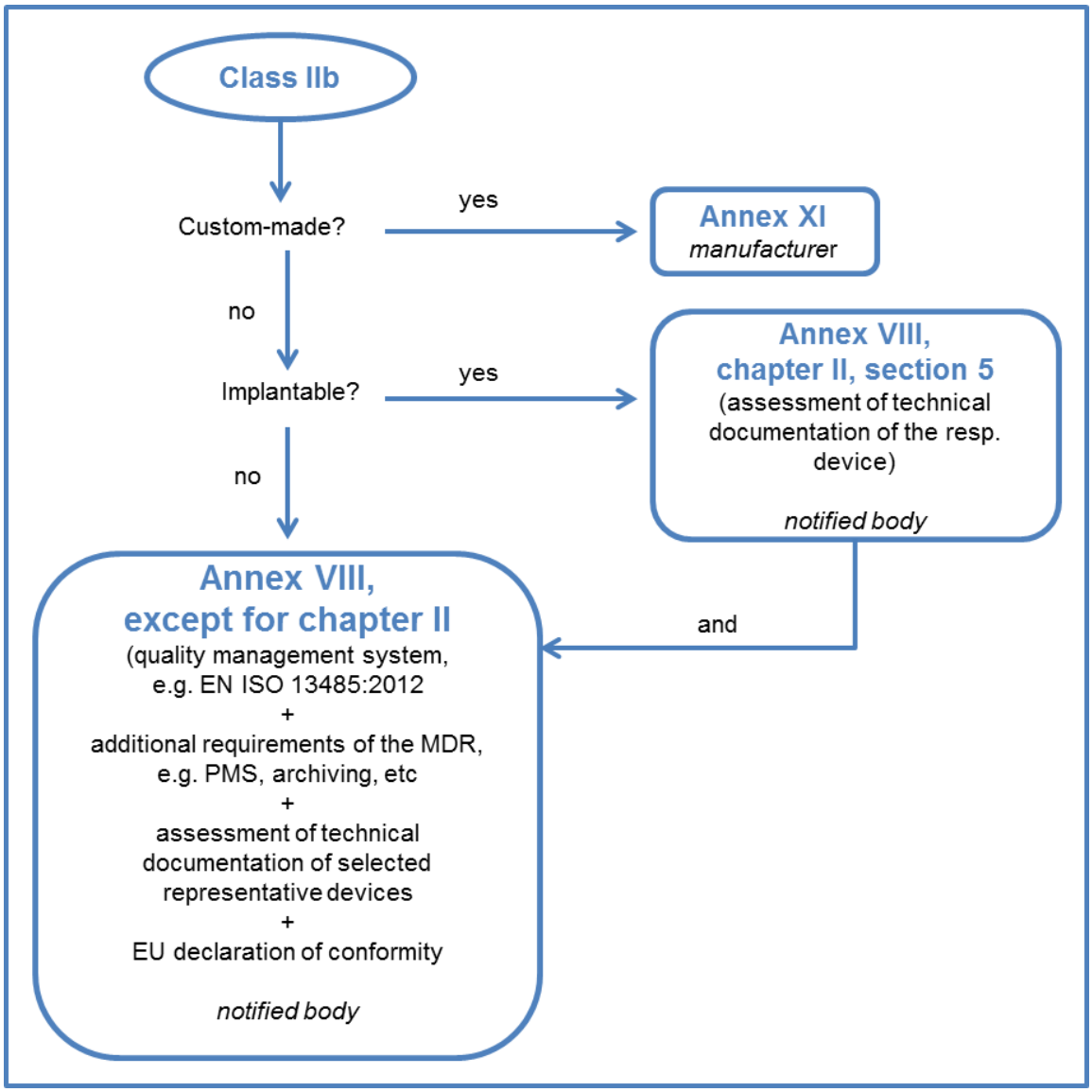

Figure 4.1-3: Conformity assessment procedure of class IIb substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text.

Substance-based devices of class III other than custom-made devices require explicit prior approval of the technical documentation and of the quality management system before the products may be placed on the market (see figure 4.1-3).

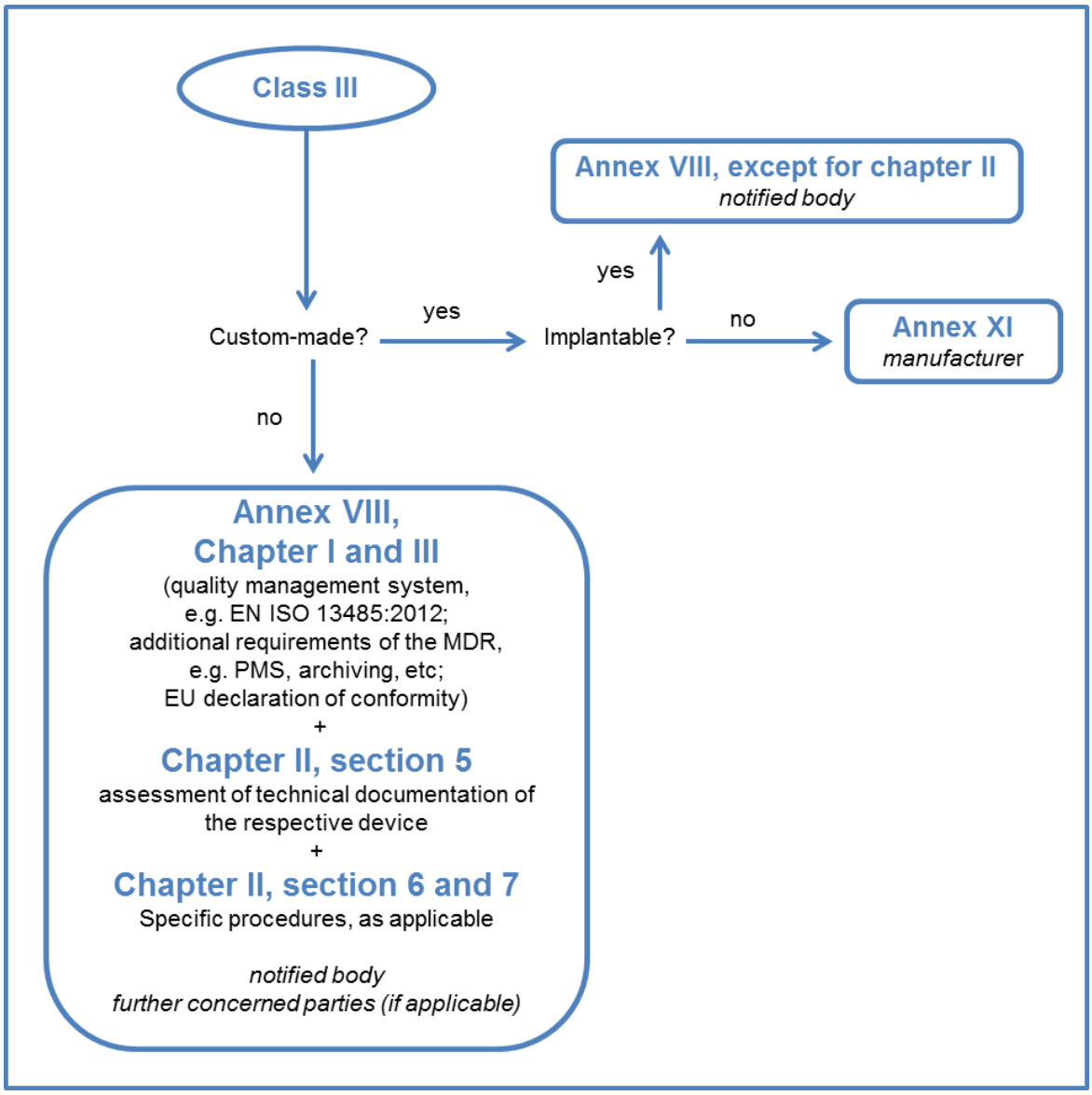

Figure 4.1-4: Conformity assessment procedure of class III substance-based medical devices according to Council`s Partial General Approach. Flow-chart by the author, further explanations in the text.

After initial certification of class IIa, IIb, or III devices, notified bodies must regularly conduct surveillance audits in the post-market phase. Certificate renewals are due after five years.

4.2 Foreseen specific procedures

In addition to the present conformity assessment procedure, several specific procedures are foreseen in Council`s MDR Partial General Approach involving further parties. These planned specific procedures would apply to certain groups of class III devices to which substance-based medical devices will frequently belong if the classification rules proposed by the Council and/or Commission will be adopted.

Moreover, additional requirements for substance-based medical devices that are absorbed by or locally dispersed in the human body are introduced by ~~the~~ Council`s partial General Agreement.

4.2.1 Clinical evaluation consultation

For **implantable devices classified as class III**, a clinical evaluation consultation procedure is proposed by the EU Council (Art. 42, paragraph 2a). An example of a substance-based medical device falling under the definition "implantable device classified as class III" is presented and discussed in section 4.3 (cross-linked hyaluronic acid intended for intra-articular injection).

The procedure of clinical evaluation consultation is described in Annex VIII, Chapter II, point 6.0. The purpose of the clinical evaluation consultation procedure is to facilitate a re-assessment of the clinical evaluation on an European level. Neither the Commission nor the European Parliament had introduced this specific procedure in their proposal or amendment, resp..

During the assessment of the technical documentation the notified body shall document the outcome of its conclusions on clinical evidence, the benefit/risk ratio, the consistency of the clinical data with the intended purpose and the Post-Market Clinical Follow-Up (PMCF) Plan in a clinical evaluation assessment report.

The assessment report is then submitted by the notified body, along with the clinical evaluation documentation of the manufacturer, to the European Commission. Scientific expert panels appointed by the Commission with expertise in the relevant medical fields and, where necessary, for categories of groups of devices, or for specific hazards (Art. 81a) then re-assess the clinical data.

Within a period of 60 days, a scientific opinion is provided by the expert panels based on the submitted documents and data. Moreover, the notified body may be requested to present its conclusions to the expert panel.

A final decision on conformity/non-conformity with the essential requirements regarding clinical evaluation can be made by the notified body only after the scientific opinion has been provided. Furthermore, it is clearly stated in Council`s Partial General Approach that the notified body shall give due consideration to the views expressed in the scientific opinion of the expert panels. In case the notified body does not follow the advice of the expert panels, the conformity assessment report must include a proper justification.

The expert panel can decide not to provide a scientific opinion. This has to be communicated to the notified body within 15 days, so that the conformity assessment procedure can be carried forward. Likewise, the notified body can proceed with the conformity assessment if no scientific opinion has been delivered within the 60 days period.

A clinical evaluation consultation is not demanded for all implantable class III devices. Exemptions comprise certificate renewal, further development of an already certified device without significant adverse effects on the benefit-to-risk ratio, or devices that comply with relevant common specifications (as defined by the Commission for a specific device group).

It is assumed that implementation of the proposed clinical evaluation consultation would be related to significant disadvantages and uncertainty for manufacturers: Since the proposed clinical evaluation consultation cannot be conducted before the notified body has compiled its assessment report, it is anticipated that a general prolongation of conformity assessment of concerned implantable class III devices would occur if this special procedure will be implemented in the final MDR. Through a deferred market launch, significant pecuniary injuries could be the consequence for manufacturers of innovative devices. To get an idea on the views of the expert panel regarding the clinical development strategy, it would be highly recommended to the manufacturers to make use of the possibility for seeking scientific advice prior starting conformity assessment (Art. 49, paragraph 1a of Council´s Partial General Approach).

4.2.2 Scrutiny procedure

In article 44 of the MDR Proposal of the Commission and Council`s Partial General Approach, a mechanism for scrutiny of certain conformity assessments is envisaged. This means that there is the possibility to re-assess the conformity of certain devices by competent authorities or the Commission after their certificates have been granted by the notified body.

The **EU Council** proposes the following: For **implantable class III devices** that have been subject to the clinical evaluation consultation procedure, the notified body shall notify the competent authorities of certificates it has granted. The notification shall be accompanied by

- A summary of safety and clinical performance
- The notified body assessment report
- Instructions for use
- The scientific opinion of the expert panel, where applicable
- A justification in case of divergent views between the notified body and the expert panel

Competent authorities and the Commission may apply further procedures and measures in case of reasonable concerns. These procedures may include, according to articles 35, 35a, 36, 37, and 69, of Council`s Partial General Approach:

- Enhanced monitoring of the notified body by the competent authority concerned
- Review and re-assessment of notified body assessments of the technical documentation and clinical evaluation documentation by the competent authority concerned
- Changes to designations and notifications
- Challenge to the competence of notified bodies by the Commission in conjunction with the Medical Device Coordination Group (MDCG)
- Evaluation regarding compliance of the device with all requirements relating to the concern of risks and non-compliances. If the competent authority comes to the result that the device presents an unacceptable risk to health and safety, they shall require the manufacturer without delay to take appropriate measures, e.g. corrective actions, restriction of marketing, withdrawal or recall from the market (article 70). Otherwise, if the risk or non-compliance is not regarded as unacceptable, it has to be resolved within a reasonable period (article 73).

The scrutiny procedure by the Council in conjunction with its foreseen clinical evaluation consultation enables the Commission and the member states to highly control implantable class III medical devices and the notified bodies that issue the technical documentation assessment certificates (known as design examination certificates in the MDD).

Nevertheless, regarding a scrutiny procedure, Council`s Partial General Approach is not as widespread as **Commission`s Proposal**, which includes a scrutiny procedure for all **class III devices** including class III substance-based medical devices.

In contrast, the **European Parliament** has refused the scrutiny mechanism after certification as introduced by the Commission and has adopted instead an assessment procedure on an European level prior certification in specific cases. **Certain high-risk devices**, namely implantable class III devices, class IIb devices intended to administer and/or remove a medicinal product, and devices manufactured utilising material of human or animal origin (except for certificate renewal and or supplement applications), have been listed (Art. 44a of EP`s MDR Amendment).

With regard to claimed high-risk devices including those named in Art. 44a, and class III devices in general, only special notified bodies shall be allowed to conduct conformity assessments (Art. 43a of EP`s MDR Amendment). If the special notified body receives an application for conformity assessment of a new device falling under Art. 44a, it shall notify the EU Commission, which transfers the application to the MDCG. This expert committee may decide within 20 days to request further documentation from the special notified body for an assessment that has to be finished before the notified body can grant the certificate.

If the special notified body does not agree with the expert committee opinion, it may once request a re-examination of the opinion.

Interestingly, in this foreseen assessment procedure in specific cases, the final decision on conformity of the new device is made by the MDCG. In the case of a favourable MDCG opinion, the special notified body may proceed with the certification. In the case of an unfavourable opinion, the special notified body shall not yet deliver the certificate of conformity (but new information can be submitted leading to a re-assessment if the information is substantially different to those data previously submitted).

4.2.3 Consultation procedure for drug-device combination products

A consultation procedure has to be conducted when a device incorporates an active substance with a pharmacological, metabolic, or immunological effect, ancillary to that of the device. Quality, safety, and usefulness of the ancillary active substance have to be evaluated by a competent authority of a Member State, or the EMA (in case of substances falling in the scope of Regulation (EC) No 726/2004).

Many substance-based medical devices contain such an active substance with ancillary pharmacological, metabolic, or immunological action: e.g. devices for synovial viscosupplementation that also contain an ancillary local anaesthetic, lozenges containing polyhexanide for an ancillary antimicrobial action, and many others.

The principle of the consultation has not been changed in Commission`s MDR Proposal, EP´s Amendment, and Council`s Partial General Approach compared with the current MDD. However, the procedure has been described more precisely (see Council`s Partial General Approach, Annex VIII, Chapter II, point 6.1).

In the MDD, the maximum time that can be taken for dossier evaluation by the competent authority or EMA, respectively, is not determined. In some cases, this leads to extremely long consultation phases within the conformity assessment procedure, and to deferred device certification. Thus, in the MDR Proposals, timelines for the authority evaluation has been suggested according to the duration of marketing authorisation procedures of medicinal products in the EU. To provide their opinion, a period of 150 days has been introduced by the Commission, which has been changed to 210 days in Council`s Partial General Approach.

Contrarily to the MDD, it is explicitly stated in the MDR Proposals that the notified body shall not deliver the certificate if the scientific opinion of the competent authority or EMA is unfavourable.

4.2.4 Procedures for devices incorporating materials of biological origin

The scope of the foreseen MDR comprises – in line with the MDD – devices manufactured utilising tissues or cells, or their derivates, of **animal origin**, which are non-viable or rendered non-viable only.

Substance-based medical devices are relatively often affected by the provisions on materials of animal origin, when, for example,

- gelatine capsules are used
- the substance or other components are produced in micro-organisms, their culture medium contains any material of animal origin (e.g. foetal calf serum)
- the substance itself or other components are of animal origin (e.g. hyaluronic acid extracted from rooster combs, collagen from bovine, ovine, or porcine sources)

Regarding requirements on non-viable materials of animal origin, the MDR Proposals reference the current MDD (e.g. Annex VIII, Chapter II, point 6.2, paragraph e of Council`s Partial General Approach). Therefore, the existing procedures are considered to be maintained.

All substances, tissues, and cells used in the manufacturing process or in the devices themselves that carry the potential risk of transmission of prions causing TSE ("Transmissible Spongiform Encephalopathies") underlie Commission Regulation (EU) No 722/2012 [27]. These include materials originating from bovine, ovine and caprine species, deer, elk, mink and cats.

During the conformity assessment, the notified body shall evaluate if the material falling under the a.m. Regulation is properly controlled, i.e. justification for use, adequate risk management, control of manufacturing from sourcing to the finished product, results of elimination or inactivation studies etc. Before issuing the certificate, the notified shall consult the competent authorities of all Member States and shall give due consideration to any comments received (Art. 5 of Regulation 722/2012).

In derogation from the described procedure, collagen, gelatine and tallow used for the manufacturing of medical devices shall meet at least the requirements as fit for human consumption laid down in Regulation (EC) No 1069/2009 [28] (Art. 1, paragraph 3 of Regulation 722/2012).

Animal material that is not covered by Regulation 722/2012, e.g. porcine material, still has to fulfill the respective essential requirements on material of biological origin. For this purpose, the harmonised standard series EN ISO 22442 [29-31] has to be followed by the manufacturer, unless otherwise justified. Compliance with these standards is assessed by the notified body.

The MDD does not apply to products incorporating or derived from tissues or cells of **human origin**, except for devices incorporating a human blood derivate within the meaning of Article 1 of Directive 2001/83/EC, with action ancillary to that of the device (Art. 1, paragraph 5, subparagraph f of the MDD). Interestingly, non-viable material of human

origin has been included in the scope of the MDR Proposals. An intended specific procedure prior certification is described in Annex VIII, Chapter II, section 6.2, paragraphs a to d that comprises seeking a scientific opinion from one of the competent authorities designated by the Member States in accordance with Directive 2004/23/EC [32].

4.2.5 Procedures for substance-based medical devices that are absorbed by or locally dispersed in the human body

The EU Council introduced a specific conformity assessment procedure for substance-based medical devices in Annex VIII, Chapter II, point 6.3.

Concerning devices falling under their proposed classification rule 21, the Council proposes the following:

"For devices that are composed of substances or combinations of substances that are intended to be introduced into the human body via a body orifice, or applied on skin and that are absorbed by or locally dispersed in the human body*, the quality and safety of the device shall be verified where applicable and limited to the requirements not covered by this Regulation, in accordance with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions."*

Although not specifically named, according to Directive 2001/83/EC, the non-clinical safety evaluation also includes an evaluation of impurities and metabolites (2001/83/EC, Annex I Part I point 2.4).

As no involvement of a third party is planned for assessment of compliance with Annex I of Directive 2001/83/EC concerning of the a.m. devices, this would be the task of the notified body.

The proposed text has to be read in conjunction with a proposed essential requirement addressing substance-based medical devices (Annex I, point 9.2 of Council`s Partial General Approach). Although the intention is considered similar, the wording slightly differs resulting in a further expansion of the requirements expressed above:

*"**Devices that are composed of substances or combinations of substances that are intended to be introduced into the human body, and that are absorbed by or locally dispersed in the human body** shall comply, where applicable and limited to the aspects*

not covered by this Regulation, with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions, as laid down in the applicable conformity assessment procedure in this Regulation."

As the requirement "introduced into the human body" is not further specified, this essential requirement is considered to apply to all substance-based medical devices that are introduced to the human body via a body orifice and to substance-based medical devices that are introduced into the human body via a surgically invasive procedure. Thus, substance-based medical devices that are absorbed by or locally dispersed in the human body and that are falling under the proposed classification rules 6, 7, 8, (general classification rules for surgically invasive devices) or rule 21 would be obliged to demonstrate conformity with this essential requirement within the conformity assessment procedure.

In summary, if the proposed wording of the Council will be implemented in the future MDR, substance-based medical devices with absorption or local dispersion in the human body, nearly independent of the route of administration (via body orifice, or surgical invasive), i.e. devices of risk classes III, IIb, and even IIa, could be affected by the requirement to demonstrate conformity with applicable parts of Annex I of Directive 2001/83/EC.

A modified essential requirement for substance-based medical devices concerning demonstration of compliance with Annex I of Directive 2001/83/EC had already been included in Commission`s Proposal but not in the proposed Amendment of the EU Parliament. However, the Commission limited the devices potentially affected to those falling under their proposed classification rule 21, i.e. substance-based medical devices that are intended to be ingested, inhaled, or administered rectally or vaginally.

Importantly, a further consultation procedure at a competent authority or the EMA is proposed by the Council in Annex VIII, Chapter II, point 6.3 for a specific subgroup of **substance-based medical devices**:

*"For devices, or their products of metabolism, that are **absorbed by the human body in order to achieve their intended purpose**, the notified body shall seek a scientific opinion from one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC […] or the […] EMA, acting particularly through its Committee on Human Medicinal Products in accordance with Regulation (EC) No 726/2004, on the*

compliance of the device with the relevant requirements laid down in Annex I of Directive 2001/83/EC."

The consulted authority should provide its scientific opinion within 150 days and the notified shall give due consideration to the views expressed in the opinion.

It has to be noted that in the latter case the reference to Annex I of Directive 2001/83/EC is not limited to safety aspects. Thus, even quality and performance/efficacy of the device shall be assessed by the competent authority or EMA on the basis of medicinal product requirements. In summary, although concerned products would be still regulated under the medical device regulation, requirements on the CE-mark application would resemble in large parts those of a marketing authorisation application of a medicinal product. An example of an affected device is given in section 3.4.1.

Directive 2001/83/EC [6] in conjunction with Regulation (EC) No 726/2004 [33] are the key legal acts in the regulation of medicinal products in the EU. For medical devices not containing a substance with ancillary pharmacological, immunological, or metabolic action, the MDR Proposal of the Commission and Council`s Partial General Approach to a MDR reference for the first time the medicinal product legislation concerning requirements on medical devices.

4.3 Example: presentation of a potential "worst-case conformity assessment scenario" of a substance-based medical device

As an example of a potential "worst-case conformity assessment scenario" of a substance-based medical device based on Council`s MDR Partial General Approach, a **device for viscosupplementation consisting of hyaluronic acid** in arthritic joints is discussed in this section.

Hyaluronic acid (HA) is a mucopolysaccharide occurring naturally in all living organisms. This non-sulphated glycosaminoglycan is composed of repeating polymeric disaccharides D-glucuronic acid and N-acetyl-D-glucosamine linked by a glucuronidic b (1→3) bond. The disaccharide units are then linearly polymerised. One HA molecule can consist of thousands of disaccharide units with a total molecular weight up to several million Daltons. The structure of HA is conserved throughout all species. Hyaluronic acids used in current products are either of animal origin (derived from rooster combs) or produced in *Streptococcus* species by fermentation.

Viscosupplementation is a medical concept that has as its therapeutic goal the restoration of rheological homeostasis in pathological structures such as osteoarthritic joints. When the normal viscoelasticity of a solid tissue compartment or the elastoviscosity of a liquid tissue compartment is decreased under pathological conditions, normal function and regenerative processes are impaired. By introducing viscosupplementary devices, the normal rheological state of such compartments is restored or augmented. These devices stay in the tissue compartment for various periods of time, depending on the nature of the viscosupplement and the pathophysiology of the tissue compartment. [34]

To slow down the endogenous degradation in the joint cavity, the hyaluronic acid chains normally are chemically stabilised through cross-linking. Depending on the degree of cross-linking and the cross-linker used, cross-linked HA remains in the joint cavity for >30 days.

HA products for viscosupplementation are usually supplied pre-filled in syringes. The cross-linked HA solution is injected into the joint cavity (= surgically invasive procedure, total introduction into the human body) and is intended to remain in place for at least 30 days after the procedure. Although the HA solution is slowly degraded and absorbed over time, the criteria of an implantable device according to Art. 2, paragraph 5 of Council`s Partial General Approach are fulfilled.

"'Implantable device' means any device, including those that are partially or wholly absorbed, which is intended

- *to be totally introduced into the human body or*
- *[…]*

by clinical intervention and which is intended to remain in place after the procedure."

Concerning device classification, rule 8, third indent, is applicable determining the product under discussion as class III device.

Thus, under the provisions of Council`s Partial General Approach to a MDR, a device consisting of cross-linked HA, which is intended to be used for viscosupplementation in arthritic joints, is an **implantable class III** device.

The device would be subject to the **clinical evaluation consultation** at respective scientific expert groups of the EU Commission during the conformity assessment procedure.

Furthermore, in case of reasonable concerns, competent authorities and the Commission could make use of further procedures and measures within the legal framework of the **scrutiny** mechanisms once the product would have been successfully certified.

As the device under discussion is a substance-based medical device that is intended to be introduced into the human body and that is absorbed by the human body, the **specific essential requirement** on the respective medical devices also applies. Kinetics, toxicity and interaction data as demanded in Annex I of Directive 2001/83/EC would have to be provided by the manufacturer. The data would have been assessed by the notified body within its conformity assessment.

If – as a further assumption – the device would contain an anaesthetic substance, e.g. lidocaine, with a pharmacological effect ancillary to that of the HA solution, a **consultation procedure** of the ancillary active substance at a competent authority would become necessary.

Today, HA used for medical devices is mainly derived from bacteria. However, the use of HA of **animal origin** (e.g. extracted from rooster combs) is still possible. In the latter case, a further assessment with focus on the "animal origin" would have to be conducted in addition to the procedures described above.

It can be concluded that, following the proposed wording of the EU Council, a CE-mark application and the subsequent conformity assessment of the device under discussion would be extremely complex. High amounts of specific data would have to be required and multiple regulatory procedures would have to be performed in parallel. From the author`s point of view the additional requirements will not increase patient`s safety in comparison to the present requirements and procedures that have to be performed with the product.

5. Discussion

5.1 Timelines

The MDR legislative procedure seems to be strongly influenced by the different political positions of the Member States. The fact that the process – which started in 2012 already – is still ongoing shows on the one hand the very complex issue and allows on the other hand the conclusion that significantly divergent positions slow down an agreement.

It has to be noted that the MDR is still in the "first reading phase". With the adoption of its Partial General Approach the Council´s official first reading has not been taken place so far. To avoid putting the complete legislative procedure at risk, it is important that trilogue discussions including members of the three involved parties are finalised before the MDR enters the "second reading phase".

According to the general requirements on an European legislative procedure, the European Parliament has to conduct its second reading within three months after the Council´s first reading. If the Members of the European Parliament approve the position of the European Council with an absolute majority in the course of the second reading the regulation will have been adopted. If the Parliament fails to take a decision within the three-month period, the legislative text in the version amended by the Council in its first reading becomes valid. If the European Parliament rejects the Council position with a majority, the complete legislative procedure failed. It is possible that the European Parliament further amends the Council´s text; in the latter cases, a second reading in the European Council becomes necessary, potentially followed by so-called conciliation committee discussions if the Parliament´s position of its second reading is not adopted by the Council [35].

Concerning the ongoing MDR legislative procedure, on 7th December 2015, a European Council meeting was held in Brussels. The Luxembourg presidency informed the ministers on the state of play of the discussions with the European Parliament. Several trilogue and technical meetings were conducted by end of 2015. Although discussions had not been coming to an end, the Luxembourg Presidency is convinced that "*the ground has been laid for an agreement between the Institutions*" [36].

Nevertheless, while it has to be noted that nothing is agreed until everything is agreed [36], predictions on the timelines of the MDR legislative procedure and the time the final legal act will be adopted can be a rough estimate only. Moreover, trilogue meetings are held in

camera. Current estimations available come from more or less unofficial sites. For example, the notified body TÜV Rheinland published a white paper (dated 2015-11-05) on its homepage [35]. The authors assessed the situation as follows: "*The final draft regulations are expected by spring 2016. This means that the legislative texts could enter into force in the autumn of 2016, provided the European Parliament agrees to the Council's proposal in its second reading*".

Others evaluate the situation less optimistic. The blogger Erik Vollebregt [37] published his assessment on 30th November 2015. "*It seems more and more likely by now that the parties in the trilogue will not be able to arrive at an agreement that would allow a final text to be published during or right after the Dutch presidency first half of 2016. The Parliament and the Council still have differences of opinion that are still very pronounced*" [37].

5.2 Implementation of proposed changes concerning substance-based medical devices

5.2.1 Demarcation / Scope

5.2.1.1 Devices containing living organisms

Living organisms, in particular *Lactobacillus spp*., are not consistently regulated in the EU today, when used for medical purposes. Uncertainty concerning their principal mode of action reflects their status as medical device in some countries and as medicinal product in others. The legitimacy of this way has been approved by the European Court of Justice in 2013 [38].

The EU Council, following the suggestion of the Commission, broadly wants to exclude devices containing living organisms from the scope of the MDR. Although the Parliament has proposed a less definitive wording, it is doubtful that in future products containing living organism can be medical devices.

5.2.1.2 Dermal fillers

Injectable dermal fillers consisting of hyaluronic acid, collagen, and other substances are mostly used as aesthetic products. It is an established procedure for years to regulate

these products as medical devices, although they are not specifically covered by the scope of the MDD.

There is now consensus in the three legislative institutions concerning the inclusion of aesthetic products without an intended medical purpose into the scope of the MDR.

Thus, the status of dermal fillers as substance-based medical devices is considered to be assured.

5.2.2 Re-classification

5.2.2.1 Rule 3

In contrast to the Commission and the European Parliament, the Council has proposed to re-classify substance-based medical devices used in direct contact with human cells, tissues, organs, or with human embryos before their implantation or administration as class III.

Information on the trilogue meetings – which is generally rather scarce – has not given any hints with regard to inclusion or not of this provision on substance-based medical devices in the intended MDR. Revised rule 3 does not seem to be a major issue in the discussions between Commission, Parliament, and Council.

As discussed in section 3.1.1, the potential impact on substance-based medical devices that would have to be re-classified through rule 3 is assessed as low. Products currently available on the European Market are barely affected.

5.2.2.2 Rule 13

Devices that include a substance, which, if used separately, would be considered to be a medicinal product, and which exerts a pharmacological, immunological, or metabolic effect ancillary to that of the device, are regulated as class III drug-device combination products according to classification rule 13. This approach is well-established. However, according to the MDD, devices shall come within the provisions of rule 13 only if the ancillary substance is *"liable to act on the human body".*

In the past, the regulatory interpretation of this clause partly varied between Member States, and has led to different decisions regarding classification as drug-device combination product or not in few cases.

Compared to the MDD, in classification rule 13, the exclusion of the clause *"which is liable to act on the human body"* can be found in all three MDR Proposals. As this classification rule seems not to be subject to further discussions in the institutions, the adoption of revised rule 13 can be expected.

As a consequence, numerous substance-based medical devices would have to be re-classified as class III drug-device combination products. The wording as proposed does not take into account the amount of ancillary substance included, its intended purpose, and its scientifically justified mode of action in the respective device often correlating with concentration.

Thus, on the one hand, the potential for non-harmonised regulation of the same product in different Member States would be minimised but on the other hand, by overruling scientific knowledge, the regulatory complexity for the affected devices will tremendously increase without seeing a significant increase in product safety.

Furthermore, it has to be noted that the affected substance-based medical devices largely comprise device groups indicated for treatment of minor common diseases, e.g. symptoms of a cold, in self-care management. In several European countries, including Germany, such products are usually not reimbursable from health insurance funds by law (for further information reference is made to [39]). The increasing regulatory effort, however, is assumed to result in a price rise. Currently, it is unclear if patients would be willing and financially able to spend more on products with nearly the same benefit-risk ratio.

5.2.2.3 Rule 19

Nanotechnology is an emerging technology and its impact on the medical device industry is expected to be growing in the future.

Classification rule 19 on nanomaterial is considered to be part of the MDR Proposals in order to attempt a reflection of current concerns on the safety of nanomaterial and to account for future developments. Although the content of rule 19 is still under discussion, its inclusion in the final MDR is regarded as highly likely.

The Commission and the Council see devices containing nanomaterial, which can be released into the human´s body, as high-risk devices and want to generally classify them as class III devices. However, the Commission´s and Council´s views don´t take into account that in medical devices containing solid particulates in any form, presence of nanomaterials at least in trace amounts can barely be excluded.

Furthermore, scientific data confirm that nanomaterial of different origin differs regarding risk potential. This knowledge should be reflected in the future legislation. It would be desirable that a risk-based and practical approach regarding presence of nanomaterial in medical devices will find entrance into the final MDR.

Limiting the scope of rule 19 to devices deliberately intended to release nanomaterial into the human body as proposed by the European Parliament, is considered a step in the right direction.

Moreover, differentiating distinct classes of medical devices including substance-based medical devices is suggested as further possibility accounting for different risk levels associated with the presence of nanomaterials in these devices (e.g. invasive/non-invasive). Additionally, the initiatives to include specific requirements on nanomaterial into the standards for biocompatibility testing are highly supported.

5.2.2.4 Rule 21

According to Vollebregt, one of the important issues that lead to a delay of agreement seems to be the proposed re-classification of substance-based medical devices, that are introduced into the body via a body orifice or applied on skin and that are absorbed by or dispersed in the human body [37]. The implications of the future MDR on substance-based medical devices and, in particular, its classification rule 21 has been the key topic of the AESGP meeting on 14 – 15 October 2015, two days after the first trilogue meeting was held [5]. Industry and authority representatives participated.

Positions of the Member States largely differ but suggestions have been introduced in order to find an agreeable compromise. Vincent Houdry, Health advisor at the Permanent Representation of France to the EU, outlined that regarding rule 21 France generally does not see the necessity to differentiate the risk depending on whether a systemic absorption occurs for the intended purpose of the device or not. Nevertheless, he indicated that France would support the implementation of an exemption mechanism, e.g. in form of a list,

regulating that some substance-based medical that are of low-risk although absorbed are exempted from being classified as class III.

Judite Neves, Director at the Health Products Directorate of the Portuguese Competent Authority (Infarmed) took rule 21 as proposed by the Council already as compromise between the view of Commission and Parliament. Nevertheless, further improvements could be made, e.g. by classifying substance-based medical devices used in the nasal cavity and oral cavity as far as the pharynx as class IIa.

At the AESGP meeting, it was revealed that other Member States hold a more disparate opinion. While Italy has supported the establishment of rule 21, Matthias Neumann, Ministry of Health, Germany, emphasised that *"the difficulty to draw a line between medicinal products and medical devices does not justify the blunt classification in class III of all substance-based medical devices, and this is considered as an overregulation by the German Ministry of Health."* [5].

Based on the available information, it is estimated as likely that a classification rule specifically addressing these substance-based medical devices will be found in the final texts of the MDR. Although the definitive wording is still unknown, at least to a certain extent, the categorisation of substance-based medical devices intended for introduction into the human body via a body orifice or application on skin as high-risk devices seems to be inevitable.

Regarding classification of substance-based medical devices in the future MDR, the inclusion of the intended target location in the classification rules and a more risk-based approach would be considered as highly preferable, not only by the author.

As reliable scientific grounds for a re-classification of substance-based medical devices are scarce from the author´s and industry point of view, the final decision on rule 21 is regarded as a mostly political one.

5.2.3 Special procedures within the conformity assessment

5.2.3.1 Scrutiny procedure & clinical evaluation consultation

The implementation of a scrutiny mechanism for high-risk medical devices (class III) after successful certification has been proposed at first by the Commission.

For the European Parliament, this suggestion was not going far enough. It has been the aim of the Parliament to introduce an intensive control and surveillance of devices they categorise as high-risk. The Parliament has proposed a specific assessment of certain high-risk devices including implantable class III medical devices by an European expert committee prior certification. As it is provided in EP`s Amendment that the final decision on conformity of the concerned high-risk device is made by the expert committee MDCG (appointed by the Commission), this proposed procedure can be considered as "centralised" conformity assessment on the European level.

The scrutiny procedure as described by the Council in conjunction with its proposed clinical evaluation consultation can be regarded as compromise between the Commission´s and the Parliament´s view.

According to the EU Council, only one specific group of class III devices, namely implantable class III devices, shall be subject to a potential second conformity assessment beyond the notified body. Prior certification, by clinical evaluation consultation, scientific expert panels appointed by the Commission shall provide their opinion on the clinical evaluation (regarding clinical performance, safety, and benefit-risk ratio) of the manufacturer and the assessment made by the notified body. As second control tool, the scrutiny mechanism in case of concerns, once the devices had been certified, is additionally foreseen.

In the Council, Germany voted – as only Member State – against the foreseen additional control on a superordinate level [40]. Although Germany has strong concerns, these results demonstrate the general consensus across most Member States on the need of a scrutiny mechanism. Therefore, the implementation of scrutiny (pre- and/or post-certification) in the final MDR is expected but the details on the procedure (or combination of procedures) that ultimately will be adopted are still unknown.

5.2.3.2 Specific procedures for substance-based medical devices

The EU Council is the only institution that has proposed specific requirements on conformity-assessment for substance-based medical devices in Annex VIII. Concerning substance-based medical devices falling under their proposed classification rule 21, the Council has foreseen that they have to fulfill requirements on kinetics, interaction data, and toxicity data, as set in Annex I of the medicinal product Directive 2001/83/EC as part of the demonstration of conformity with the medical device legislation.

Unfortunately, the scope of the proposed essential requirement on substance-based medical devices is broader than that of the specific procedure described in Annex VIII, Chapter II, point 6.3. A respective harmonisation of the texts would be considered as helpful to avoid misunderstandings.

Moreover, although covered by the definition of a medical device, substance-based medical devices that are absorbed by the human body in order to achieve their intended purpose shall demonstrate compliance with all relevant requirements laid down in Annex I of Directive 2001/83/EC. Thus, data requirements would closely resemble those of medicinal products.

In general, a critical look is taken at referencing another legal framework within the future MDR. In particular, with regard to toxicity, the well-established test regimes as described in the EN ISO 10993 standard series on "biological evaluation of medical devices" [41] are considered to cover most aspects of interest for substance-based medical devices as well.

Based on the available information no reliable estimation can be provided on the likeliness of inclusion of these special provisions into the final texts of the MDR. As the European Parliament refrains from the general treatment of substance-based medical devices as products of increased risks, and the requirements proposed by the Council even exceed those of the Commission, it is hypothesised that implementing all of its intended provisions will be very difficult for the Council.

5.2.3.3 Consultation for class III drug-device combinations

The principle of consultation of an active substance with ancillary pharmacological, immunological, or metabolic action, included in a medical device, at one competent authority of a Member State or the EMA, already established in the MDD, will also be implemented in the coming MDR.

To improve the consultation procedures within the conformity assessment, timelines for the first assessment round at the competent authority or EMA will presumably be included in the MDR.

This is regarded as positive signal, since European marketing authorisation procedures for medicinal products are normally performed within tight deadlines. It can be supposed that in the past – without predefined timelines for consultation procedures – the competent authorities might have set their priorities in favour of authorisation procedures.

Moreover, the authority´s position will be strengthened, since, in case of an unfavourable opinion on quality, safety or usefulness of the ancillary active substance, no certificate can be issued by the notified body.

5.2.3.4 Assessment of material of biological origin

If material of animal origin is used during manufacturing of a device or is contained in the final product, special essential requirements apply. Today, procedures are already established, with assessment of the material by the notified body, and in cases of material carrying the potential risk of TSE transmission, the competent authorities of all Member States are consulted (following the provisions of Regulation (EU) No 722/2012).

The Commission and the Council obviously regard the existing procedures as sufficient for adequate control of the potential additional risks, as they have not proposed any changes.

In 2012, the European Parliament, however, allocated devices manufactured by or containing material of animal origin to their group of certain high-risk devices, for which an assessment by a European expert group on Commission level has been proposed (Art. 43a and Art. 44a of EP`s Amendment). Taking today´s existing legislative situation into consideration, EP`s Amendment would lead to a doubled assessment/consultation on a European level of material falling under Regulation (EC) No 722/2012, by the expert committee and by the competent authorities of the Member States. In light of the desirable aim to find a realistic solution, a doubled European assessment procedure should be avoided.

In contrast, the inclusion of a special assessment procedure for non-viable material of human origin seems likely if such products will be added to the scope of the MDR.

6. Conclusion and outlook

In the European Union, substance-based medical devices are often considered as high-risk product group today by the authorities, and are therefore subject to intense discussion in the ongoing legislative procedure of the MDR. Main focus appears to be on their classification and furthermore on their conformity assessment.

Taking Commission`s MDR Proposal and the amendments proposed by the European Parliament and the Council into consideration, it seems to be inevitable that, with effect from the entry into force of a MDR, a reclassification of few substance-based medical devices - in case the EU Parliament`s Amendments prevails - and many - in case Council`s Partial General Approach prevails - will become necessary.

The Presidency of the EU Council currently emphasised in an apt manner that "*nothing is agreed until everything is agreed*" [36]. Therefore, the exact future content of the MDR concerning substance-based medical devices is still incalculable in certain parts. The criticism by the industry of the fact that trilogue meetings are held in camera is understandable.

Nevertheless, with the aim to increase patients´ safety, requirements on certification of many substance-based medical devices will likely increase, particularly those categorised as class III devices. With regard to the so-called "specific conformity assessement procedures" such as a scrutiny mechanism, Council`s Partial General Approach already has to be seen as a compromise between the Commission´s and Parliament´s view. The manufacturers are strongly advised to thoroughly monitor the ongoing legislative process and to timely prepare for the upcoming changes with regard to budget and resources.

Clearly, patients`safety is a major goal in the regulation of the pharmaceuticals and medical market. However, in parallel, it should be attempted by the involved politicians to avoid over-regulation of the broad group of substance-based medical devices and to find a realistic solution that can be accomplished and implemented by the manufacturers. Additionally, market access of innovative devices shall not be unnecessarily decelerated. Otherwise, sufficient health care in Europe might be compromised.

When comparing Commission`s proposed MDR with Parliament`s amendments and Council`s General Agreement it seems for the author, that the parliamentarians provide the fewest over-regulations, but they are pressured by the Commission and the Council. Thus, the outcome of the trilogue discussions, probably published in the first or second half of 2016, is awaited with interest.

As a more general conclusion, the fact that the legislative procedure is still ongoing clearly demonstrates the complexity of the project "Medical Device Regulation". Moreover, as all aspects of a future regulation on medical devices in Europe are currently discussed in parallel, a high risk of confusion even in the legislative parties is seen. Prioritisation of the single aspects prior to starting the discussions and a subsequent step-by-step processing would be considered as helpful to avoid the implementation of not properly conceived regulatory requirements and to bring the legislative process forward.

7. Summary

Currently, the European medical device industry in under complete revision. The official legislative procedure for a Medical Device Regulation (MDR) started in 2012, and, since Proposals of all three concerned institutions (EU Commission, European Parliament, Council of the European Union) have been made available, consensus has now to be reached.

Substance-based medical devices, as an important sub-group of medical devices often regarded as high-risk products, are particularly affected by proposed re-classification and specific conformity assessment procedures. The present work focuses on the implications of EU Council`s Partial General Approach to a MDR on demarcation, classification, and conformity assessment of substance-based medical devices in comparison to the current requirements as laid down in Directive 93/42/EEC (MDD), and to Commission`s MDR Proposal and European Parliament`s Amendments.

The demarcation of a substance-based medical device is usually based on the product´s principal mode of action. By way of derogation from this approach, it is discussed to exclude substance-based medical devices containing living organisms *per se* from the scope of the MDR. On the other hand, dermal fillers for aesthetic purposes will be explicitly included in the scope of the future MDR.

Classification criteria are provided by the legislator generally enabling medical devices to be appropriately classified by a risk-based approach (Annex IX of MDD 93/42/EEC and Annex VII of proposed MDR, respectively). In comparison to the classification criteria as set out in the MDD, some classification rules are proposed to be modified and new classification rules are introduced in the proposed MDR. Regarding substance-based medical devices, the potential revision of classification rules 3 and 13 and implementation of classification rule 21 (specific rule for certain substance-based medical devices) and even rule 19 on nanomaterials are of special interest. It can be concluded that in case Council`s Partial General Approach on classification will be implemented in the final legal texts of the MDR, many substance-based medical devices would have to be re-classified, and that the number of class I substance-based medical devices would be minimised.

In addition to the conformity assessment to be performed by a notified body, several specific procedures are foreseen in Council`s Partial General Approach to a MDR involving further parties. These planned specific procedures would apply to certain class III devices to which substance-based medical devices will frequently belong if the classification rules proposed by the Council and/or Commission will be adopted. In particular, the

implementation of a scrutiny mechanism for certain high-risk devices is considered likely, taking into account available information on the ongoing legislative procedure. Moreover, Annex I of Directive 2001/83/EC is referenced for requirements on kinetics, interactions, and toxicity of substance-based medical devices if they are introduced into the human body and they, or their products of metabolism, are systemically absorbed or locally dispersed. And because obviously there will be no further explanations or definitions concerning the term “systemically absorbed” it is to anticipate, that some authorities see already a systemically absorption only if some molecules of the product or its excipients are absorbed, even if the intended action of the medical device doesn`t need its systemic absorption.

Substance-based medical devices, and particularly their proposed re-classification, are issues with highly divergent views throughout the legislative institutions and the Member States. Thus, since "*nothing is agreed until everything is agreed*" [36], and the trilogue discussions had not been coming to an end by end of 2015, only preliminary estimations can be given on the content of the future MDR with regard to demarcation, classification, and conformity assessment of substance-based medical devices. Nevertheless, finding an outweighed and realistic approach should the aim.

Taking the slow progress of the ongoing legislative procedure into account, according to the author´s opinion, a step-by-step processing of the most urgent regulatory aspects during the discussion in and between the legislative institutions would have resulted in the existence of decisions for at least some of the most important issues.

8. References

1. *COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices, OJ L 169 of 12.7.1993, p. 1, last revised by Art. 1 of Directive 2007/47/EC of the European Parliament and the Council of 5.9.2007 (OJ L 247 of 21.9.2007, p. 21).*

2. European Commission, *Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 - COM(2012) 542 final*, in *2012/0266 (COD)*. 2012: Brussels, 26 September 2012.

3. European Parliament, *Amendments adopted by the European Parliament on 22 October 2013 on the proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (COM(2012)0542 – C7-0318/2012 – 2012/0266(COD))*, in *P7_TA(2013)0428*. adopted 2014-04-02.

4. Council of the European Union. *Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, Interinstitutional File 2012/0266 (COD), 12040/1/15 REV 1 PHARM 36 SAN 281 MI 567 COMPET 410 CODEC 1193, Brussels, 21 September 2015;*. 2015 2015-12-30]; Available from: http://www.consilium.europa.eu/de/press/press-releases/2015/09/23-medical-devices/.

5. AESGP. *Conference Report - Substance-based medical devices: an important part of self-care, Brussels, 14-15 October 2015*. 2015 2015-12-26]; Available from: http://www.aesgp.eu/media/reports/Conference_report_-_FINAL.pdf.

6. *DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67, lastly revised Directive 2012/26/EU of the European Parliament and of the Council of 25.10.2012 (OJ L299, 27.10.2012, p. 1)*.

7. Anhalt, E., *Lactobacillus-haltige Produkte im Spannungsfeld Arzneimittel-Medizinprodukte - Erläuterung von Metabolismus bzw. metabolischen Reaktionen aus biochemischer Sicht.* MPR, 2009(4): p. 127-131.

8. European Parliament. *REPORT on the proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (COM(2012)0542 – C7-0318/2012 – 2012/0266(COD)) - Committee on the Environment, Public Health and Food Safety - Rapporteur Dagmar Roth-Behrendt - Doc-No. A7-0324/2013*. 2013 2015-10-30]; Available from: http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2013-0324&language=EN.

9. Borges, S., J. Silva, and P. Teixeira, *The role of lactobacilli and probiotics in maintaining vaginal health.* Arch Gynecol Obstet, 2014. **289**(3): p. 479-89.

10. Atassi, F., et al., *Vaginal Lactobacillus isolates inhibit uropathogenic Escherichia coli.* FEMS Microbiol Lett, 2006. **257**(1): p. 132-8.

11. Atassi, F. and A.L. Servin, *Individual and co-operative roles of lactic acid and hydrogen peroxide in the killing activity of enteric strain Lactobacillus johnsonii NCC933 and vaginal strain Lactobacillus gasseri KS120.1 against enteric, uropathogenic and vaginosis-associated pathogens.* FEMS Microbiol Lett, 2010. **304**(1): p. 29-38.

12. Kemgang, T.S., et al., *Cross-talk between probiotic lactobacilli and host immune system.* J Appl Microbiol, 2014. **117**(2): p. 303-19.

13. European Commission, *MEDDEV 2.1/3 rev 3 - Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative*. 2009, DG ENTERPRISE and INDUSTRY, Directorate F, Unit F3 "Cosmetics and medical devices".

14. *REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 30 November 2009 on cosmetic products (recast), OJ L 342, 22.12.2009, p. 59, lastly revised COMMISSION REGULATION (EU) No 1004/2014 of 18 September 2014 (OJ L 282, 26.9.2014, p. 5)*

15. European Commission's Borderline and Classification Medical Devices Expert Group. *MANUAL ON BORDERLINE AND CLASSIFICATION IN THE COMMUNITY REGULATORY FRAMEWORK FOR MEDICAL DEVICES - Version 1.17*. 2015 2015-12-30]; Available from: http://ec.europa.eu/growth/sectors/medical-devices/specific-areas-development/index_en.htm.

16. Anhalt, E., *Bedürfen Medizinprodukte mit Arzneimittelanteil immer eines Konsultationsverfahrens?* MPJ, 2007. **14**(4): p. 196-197.

17. Proksch, E. and H.P. Nissen, *Dexpanthenol enhances skin barrier repair and reduces inflammation after sodium lauryl sulphate-induced irritation.* J Dermatolog Treat, 2002. **13**(4): p. 173-8.

18. Heise, R., et al., *Dexpanthenol modulates gene expression in skin wound healing in vivo.* Skin Pharmacol Physiol, 2012. **25**(5): p. 241-8.

19. Alban, S., *Kapitel 14 - Kohlenhydrate II: Polysaccharide und Polysaccharidderivate*, in *Hänsel Sticher Pharmakognosie Phytopharmazie*, O. Sticher, J. Heilmann, and I. Zündorf, Editors. 2015, Wissenschaftliche Verlagsgesellschaft mbH: Stuttgart. p. 350-439.

20. HMPC, *Assessment report on Cetraria islandica (L.) Acharius s.l., thallus (EMA/HMPC/36866/2014)*. 2014, EMA: London, UK.

21. FIDE European Dental Industry. *Nanomaterials and MDD Recast*. 2012 2015-11-23]; Available from: http://www.eaarmed.org/wp-content/uploads/2014/03/FIDE-Statement-Nano-and-Recast-summary-2012-09-17_final.pdf.

22. Panaceo International Active Mineral Production GmbH. *PANACEO MED Haut- und Wundpuder - Gebrauchsinformation - V20130430*. 2015-01-03]; Available from: http://www.panaceo.com/fileadmin/template01/uploads/downloads/Folder_Med_Wundpuder_OE_V20130430_Homepage.pdf.

23. Hisano, M., et al., *Cranberries and lower urinary tract infection prevention.* Clinics (Sao Paulo), 2012. **67**(6): p. 661-8.

24. Bouckaert, J., et al., *Receptor binding studies disclose a novel class of high-affinity inhibitors of the Escherichia coli FimH adhesin.* Mol Microbiol, 2005. **55**(2): p. 441-55.

25. GmbH, T.S.P.S. *Med-Info - Council Directive 93/42/EEC on Medical Devices*. 2015-10-22]; Available from: http://www.tuev-sued.de/uploads/images/1441713496633121630881/council-directives-9394eec.pdf.

26. *DIN EN ISO 13485:2012-11: Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2003 + Cor. 1:2009); German version EN ISO 13485:2012 + AC:2012*.

27. *COMMISSION REGULATION (EU) No 722/2012 of 8 August 2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin, OJ L 212/3, 9.8.2012.*

28. *REGULATION (EC) No 1069/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 October 2009 laying down health rules as regards animal by-products and derived products not intended for human consumption and repealing Regulation (EC) No 1774/2002 (Animal by-products Regulation), OJ L 300/1, 14.11.2009*.

29. *EN ISO 22442-1:2007 Medical devices utilizing animal tissues and their derivatives - Part 1: Application of risk management (ISO 22442-1:2007)*.

30. *EN ISO 22442-2:2007 Medical devices utilizing animal tissues and their derivatives - Part 2: Controls on sourcing, collection and handling (ISO 22442-2:2007)*.

31. *EN ISO 22442-3:2007 Medical devices utilizing animal tissues and their derivatives - Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents (ISO 22442-3:2007)*.

32. *DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, p. 48, 7.4.2004.*

33. *REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, p. 1, 30.4.2004*.

34. Balazs, E.A. and J.L. Denlinger, *Viscosupplementation: a new concept in the treatment of osteoarthritis.* J Rheumatol Suppl, 1993. **39**: p. 3-9.

35. TÜV Rheinland. *Revision of European legislation on medical devices*. 2015 2015-12-30]; Available from: https://www.tuv.com/media/corporate/products_1/2015-11-06_Revision_der_europaeischen_Gesetzgebung_fuer_Medizinprodukte_ENG.pdf.

36. Council of the European Union, *14215/15 - Employment, Social Policy, Health and Consumer Affairs Council meeting on 7 December 2015 - Proposal for a Regulation of the European Parliament and of the Council on medical devices and amending*

Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 - Information from the Presidency on the state of play. 2015: Brussels.

37. Vollebregt, E. *Medical devices legal and regulatory blog*. 2015-12-28]; Available from: http://medicaldeviceslegal.com/.

38. European Court of Justice, *Case C‑109/12 Laboratoires Lyocentre v Lääkealan turvallisuus– ja kehittämiskeskus, Sosiaali– ja terveysalan lupa– ja valvontavirasto: http://curia.europa.eu/juris/document/document_print.jsf?doclang=EN&text=&pageIndex=0&part=1&mode=lst&docid=142615&occ=first&dir=&cid=215880*. 2013.

39. Gemeinsamer Bundesausschuss (GBA). *FAQ - Verordnungsfähigkeit von Medizinprodukten in der Arzneimitelversorgung*. 2015-12-28]; Available from: https://www.g-ba.de/institution/sys/faq/84/. .

40. Lehmphul, M. *Scrutiny-Verfahren kaum noch abzuwenden*. 2015 2015-12-15]; Available from: https://www.medizintechnologie.de/aktuelles/nachrichten/2015-4/scrutiny-verfahren-kaum-noch-abzuwenden/.

41. *EN ISO 10993-1:2009/AC:2010 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2009)*.

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

_____

Dr. Ruth Zeller-Adam